# Antimicrobial Drug Development: Past, Present and Future

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# Introduction

- **History of antimicrobial drug discovery and development**
- **Present state of antimicrobial drug development**
  - **economic issues**
  - **scientific issues**
- **Future needs in antimicrobial drug development**
  - **surveillance**
  - **prevention and control**
  - **research**
  - **product development**

# Antimicrobial Drug Development
## *The Past*

- **Efficacy of antimicrobials compared to no treatment in serious and life threatening disease is clear**
  - **mortality of meningitis in pre-antibiotic era 70% to 90%**
  - **mortality with subcutaneous sulfanilamide in study published in 1937 was 10%**

- **Based on efficacy in serious and life-threatening disease clinicians began use of antimicrobials in less serious, self-resolving diseases**
  - **based on premise of eradication of organisms**
  - **does not take into account human immune response and natural history of largely self-resolving diseases**

# Antimicrobial Drug Development

## *The Past*

- **Majority of classes of antimicrobials were discovered by the end of the 1960's**
- **Most drugs were brought into clinical use prior to 1962 Kefauver-Harris Amendment to Food Drug and Cosmetic Act**
  - **amendment required demonstration of efficacy as well as safety of drug product**
  - **Well-designed clinical trials on efficacy and safety of antimicrobials prior to 1962 in less severe disease often lacking**

# History of Antibacterial Drug Discovery and Approval

Food Drug and Cosmetics Act 1938 →

Kefauver-Harris Amendments 1962 →

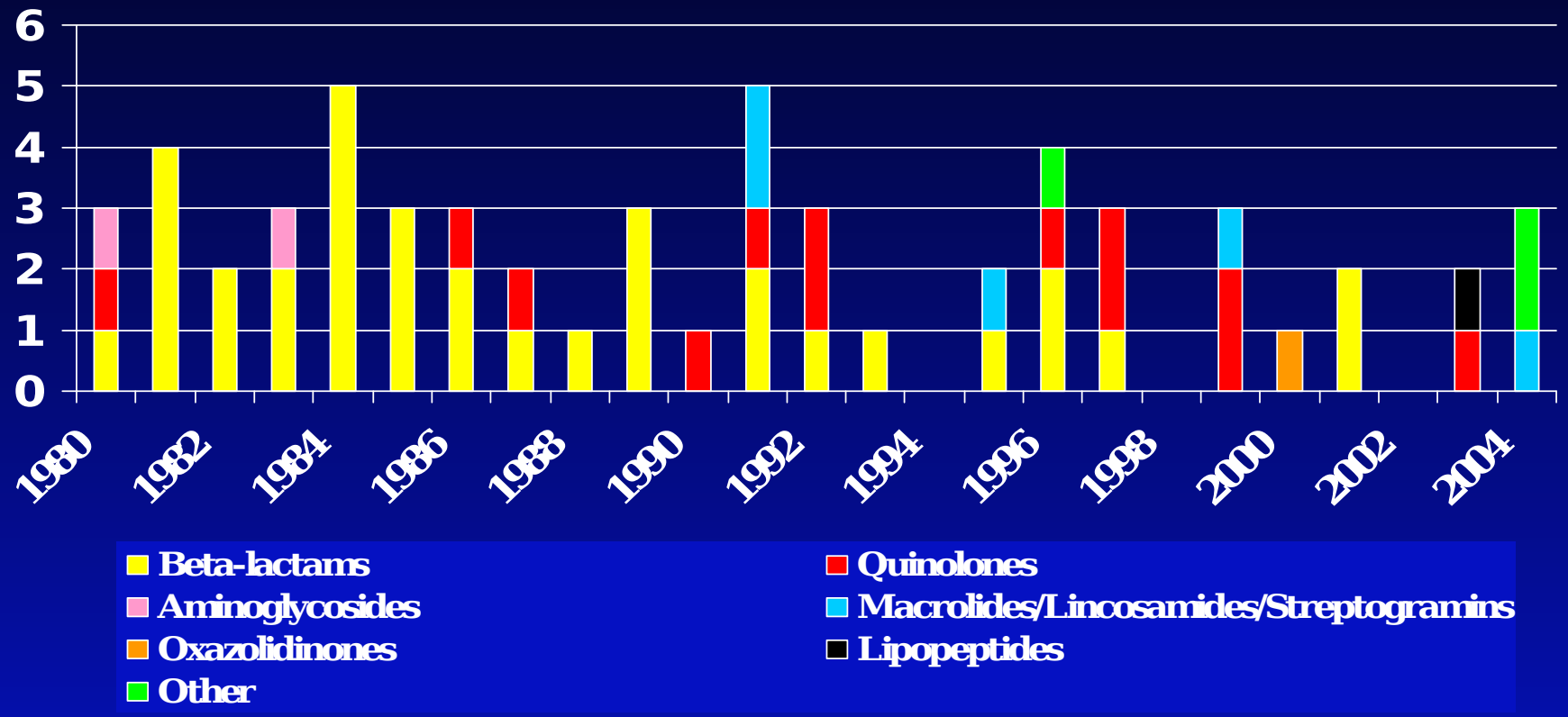
| Year Introduced | Class of drug |
|---|---|
| 1935 | Sulfonamides |
| 1941 (1945) | Penicillins (Cephalosporins) |
| 1944 | Aminoglycosides |
| 1949 | Chloramphenicol |
| 1950 | Tetracyclines |
| 1952 | Macrolides/Lincosamides/Streptogramins |
| 1956 | Glycopeptides |
| 1957 | Rifamycins |
| 1959 | Nitroimidiazoles |
| 1962 | Quinolones |
| 1968 | Trimethoprim |
| 2000 | Oxazolidinones |
| 2003 | Lipopeptides |

# Antimicrobial Drug Development
## *The Past*

- **Majority of drug development since 1960's has been alterations in previously discovered classes of drugs**
  - **increased spectrum of activity in some members of same classes**
  - **differences in pharmacokinetics allowed use in different infections (e.g. meningitis)**
  - **differences in toxicity profiles**

- **Majority of drugs in 1980's were cephalosporins and majority in 1990's were quinolones**

# Drug Approvals by Class
## *Systemic Antibacterials*



# Drug Approvals by Class
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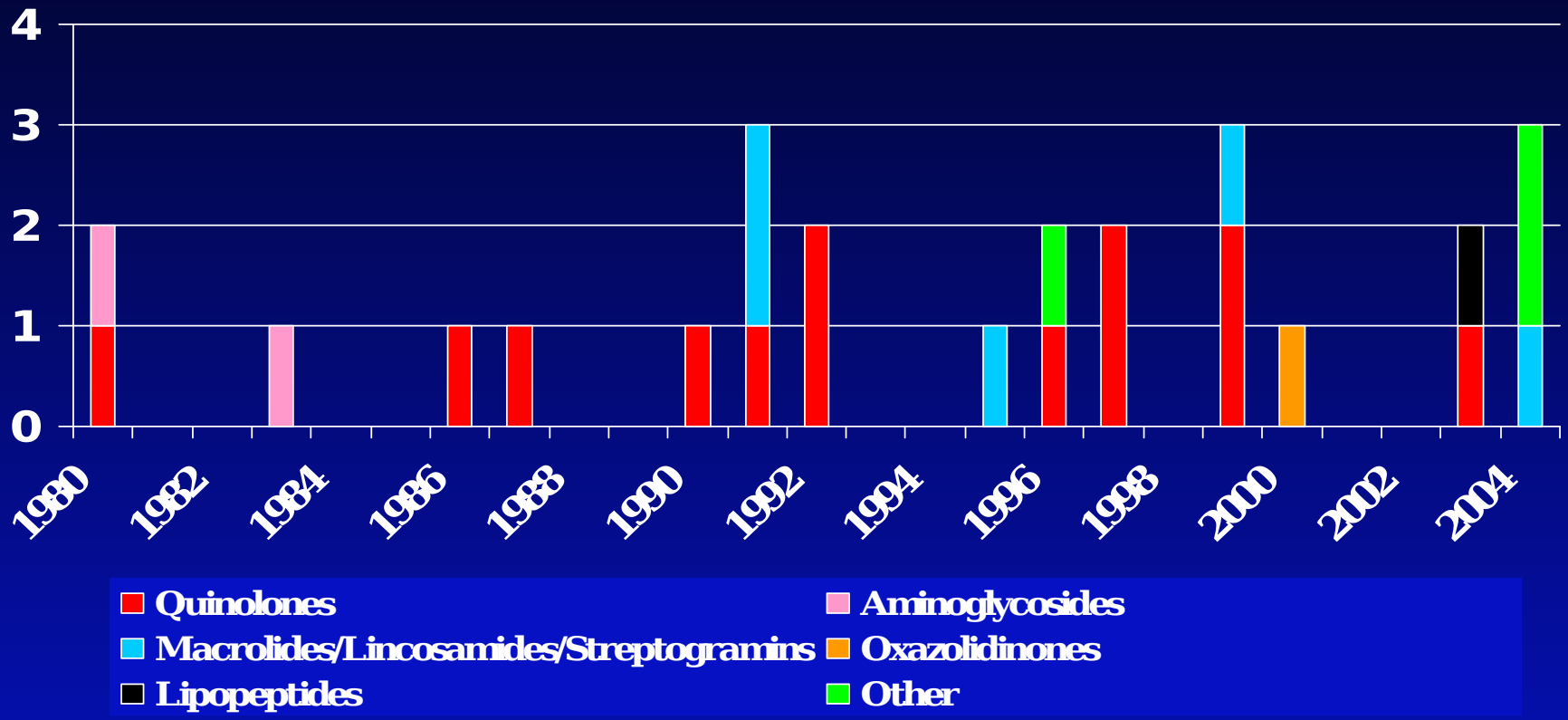


# Antimicrobial Drug Development
## *The Present*

- **Some large pharmaceutical companies have chosen to exit the area of antimicrobial drug discovery and development**
  - **issues with antimicrobial drug discovery have been present for last 40 years**
  - **few drugs to develop given failure of discovery efforts and unfulfilled promise of genomics**
- **Many of issues regarding companies decisions are based in economics**

# Antimicrobial Drug Development

## *The Present*

- **Antimicrobials not a profitable as other drug classes**
  - **third most profitable class overall behind CNS and cardiovascular drugs**
  - **best selling antimicrobial = $2 billion in 2003**
  - **Lipid lowering agent = $9 billion in 2003**

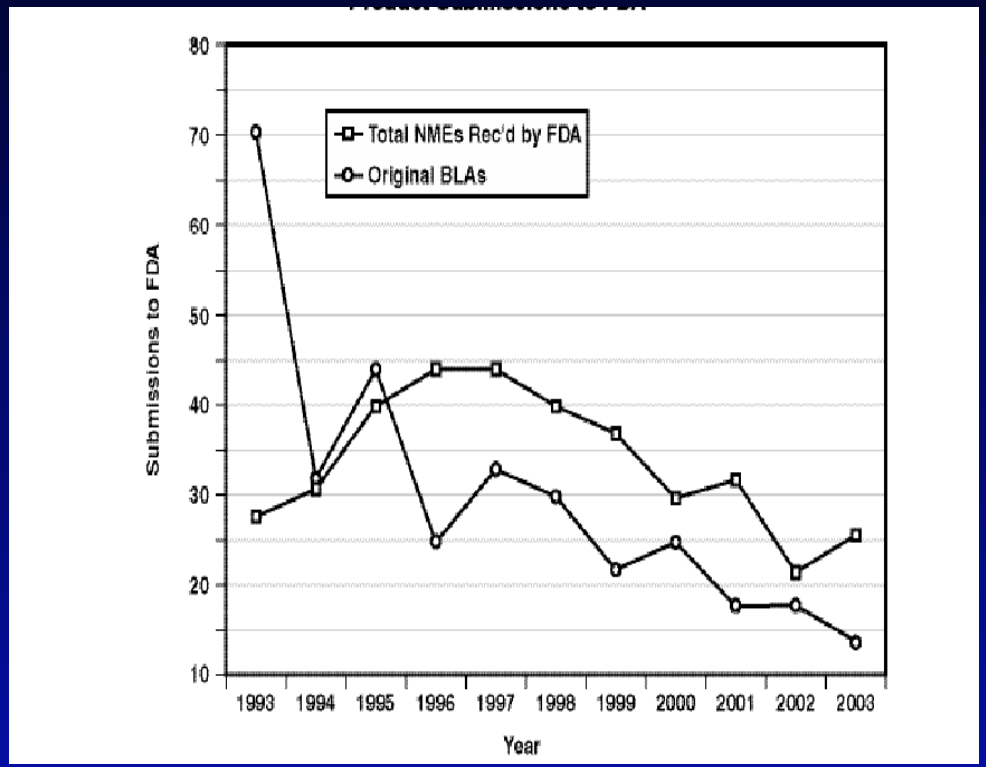
- **Economic factors**
  - **high level of competition with already marketed drugs**
  - **primarily short term treatments (vs. chronic disease)**
  - **lack of perceived need by clinicians**
  - **greatest need is for less common diseases**
  - **appropriate use limits market**

# Antimicrobial Drug Development
## *The Present*

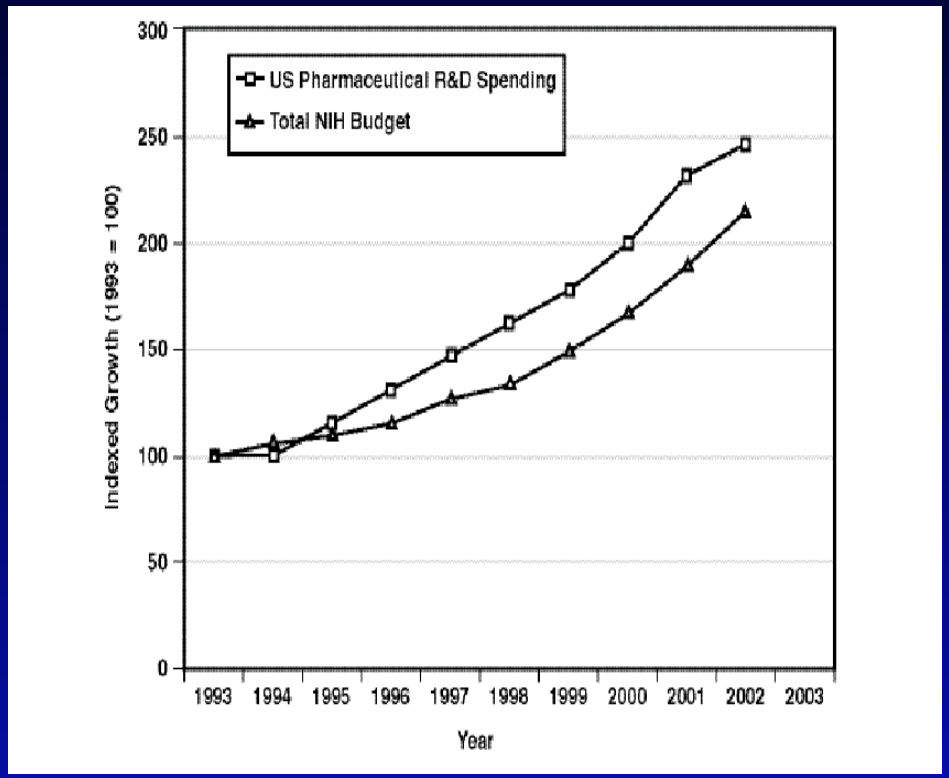
- **Scientific issues**
  - **claims of "increased regulatory hurdles" for antimicrobials reflects misunderstanding of scientific issues**
  - **"pathogen-specific" indications are not supportable scientifically given differences in natural history**
  - **Issue of increased sample size necessary to demonstrate similar efficacy of new drug to control**
    - **if new drug is superior, sample size is smaller**
    - **lack of data on magnitude of benefit in some diseases**
  - **Resistant pathogens less common in clinical trials**
  - **Clinical impact of resistant pathogens less certain in more common, self-resolving diseases**

# Antimicrobial Drug Development

## *The Present*




**Ten year trend in all new molecular entity drug submissions to FDA**




**Ten year trend in pharmaceutical co and NIH research and development s**

# Antimicrobial Drug Development

## *The Present*

- **FDA has undertaken several initiatives to streamline drug development for new drugs (and antimicrobials in particular)**
  - **Critical Path - eliminate failed drugs earlier**
- **Important to balance economic needs of companies with primary goal of protecting and advancing public health**
- **Several FDA meetings to address issues:**
  - **applying data from studies in one disease to support studies for approval in another disease**
  - **applying data from efficacy in susceptible pathogens to support approval for resistant pathogens**

# Antimicrobial Drug Development

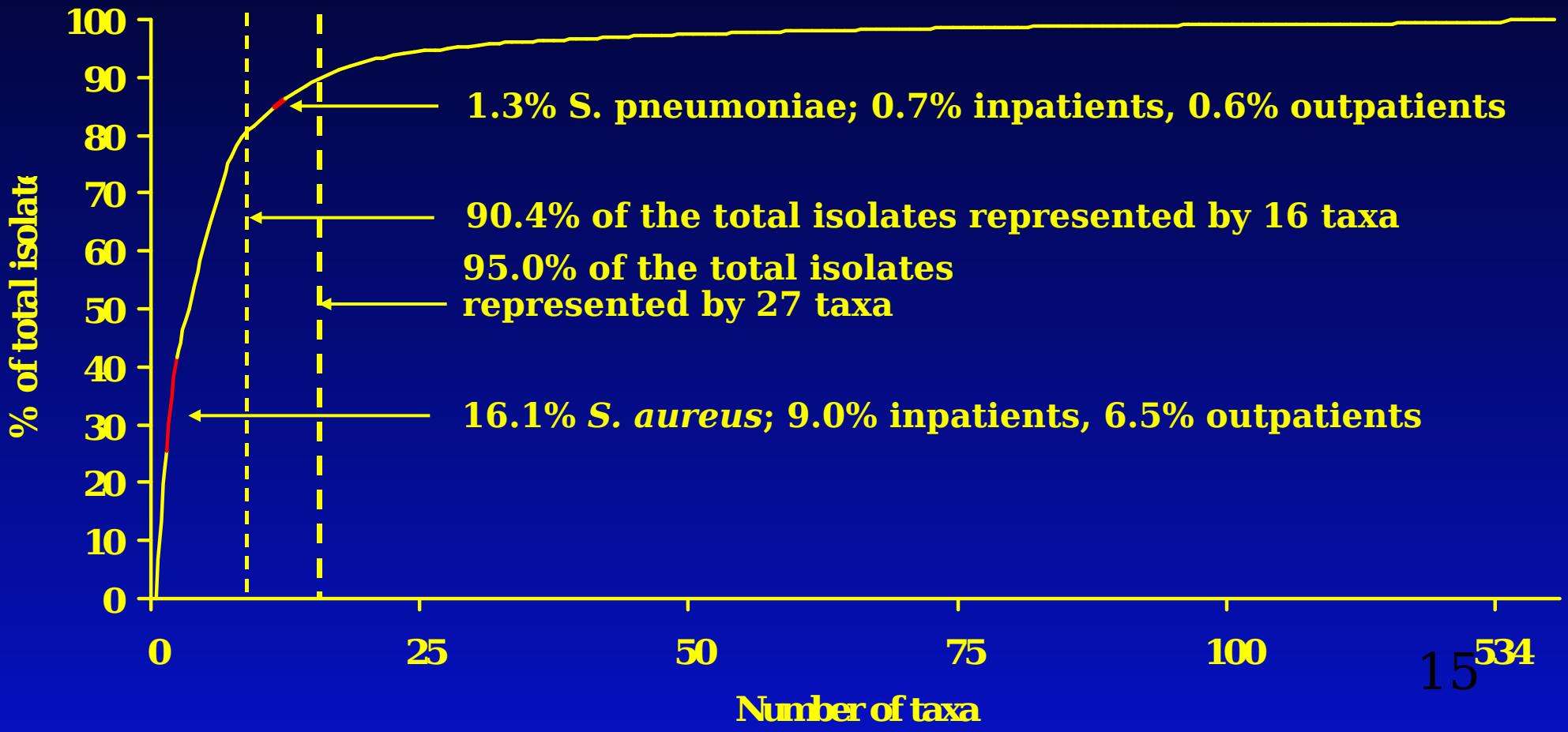
## *The Future: Surveillance*

- **FDA has obtained surveillance data on resistant pathogens to address areas of greatest public health need**

- **FDA developed criteria for pathogens of greatest public health importance**
  - **organism common enough in the population to warrant concern and to be able to study**
  - **serious and life threatening diseases**
  - **drug to which organism is resistant is used in the disease**
  - **few therapeutic options due to multi-drug resistance**
  - **clinical correlation of in vitro resistance with clinical outcomes**

# Prevalence of Clinically Relevant Species (Based on Commonly Cultured Organisms)

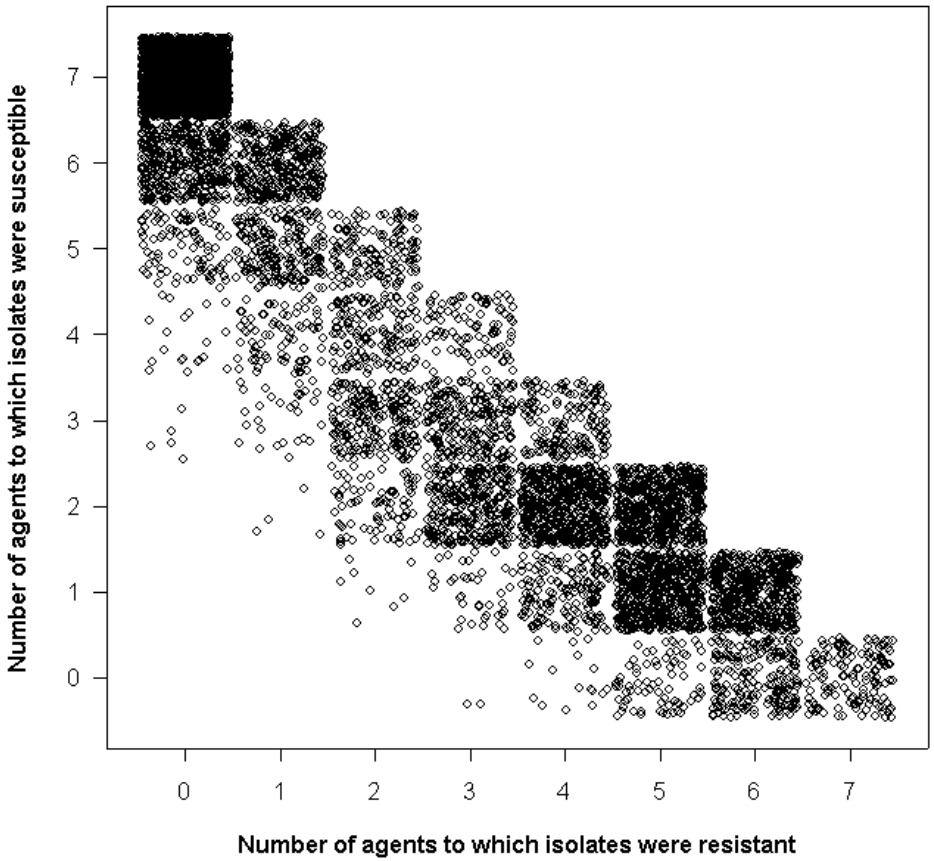
***Only 27 taxa account for 95% of clinically encountered b***
***... S. pneumoniae accounts for 1.3%***



# Evaluating MDR Trends among Species (2000-2002)

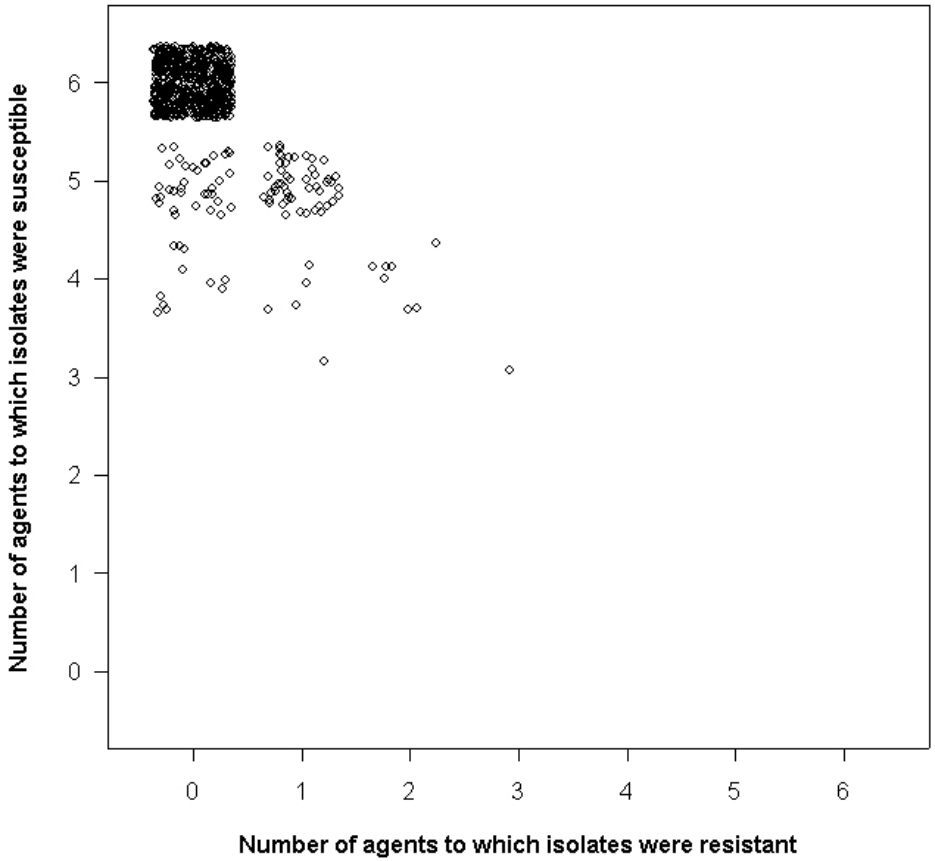
***Acinetobacter baumannii* (n = 7,914)**

**Antimicrobials = Gentamicin, Ceftazidime, Imipenem, Ciprofloxacin, Cefepime, Ampicillin-sulbactam, Piperacillin**

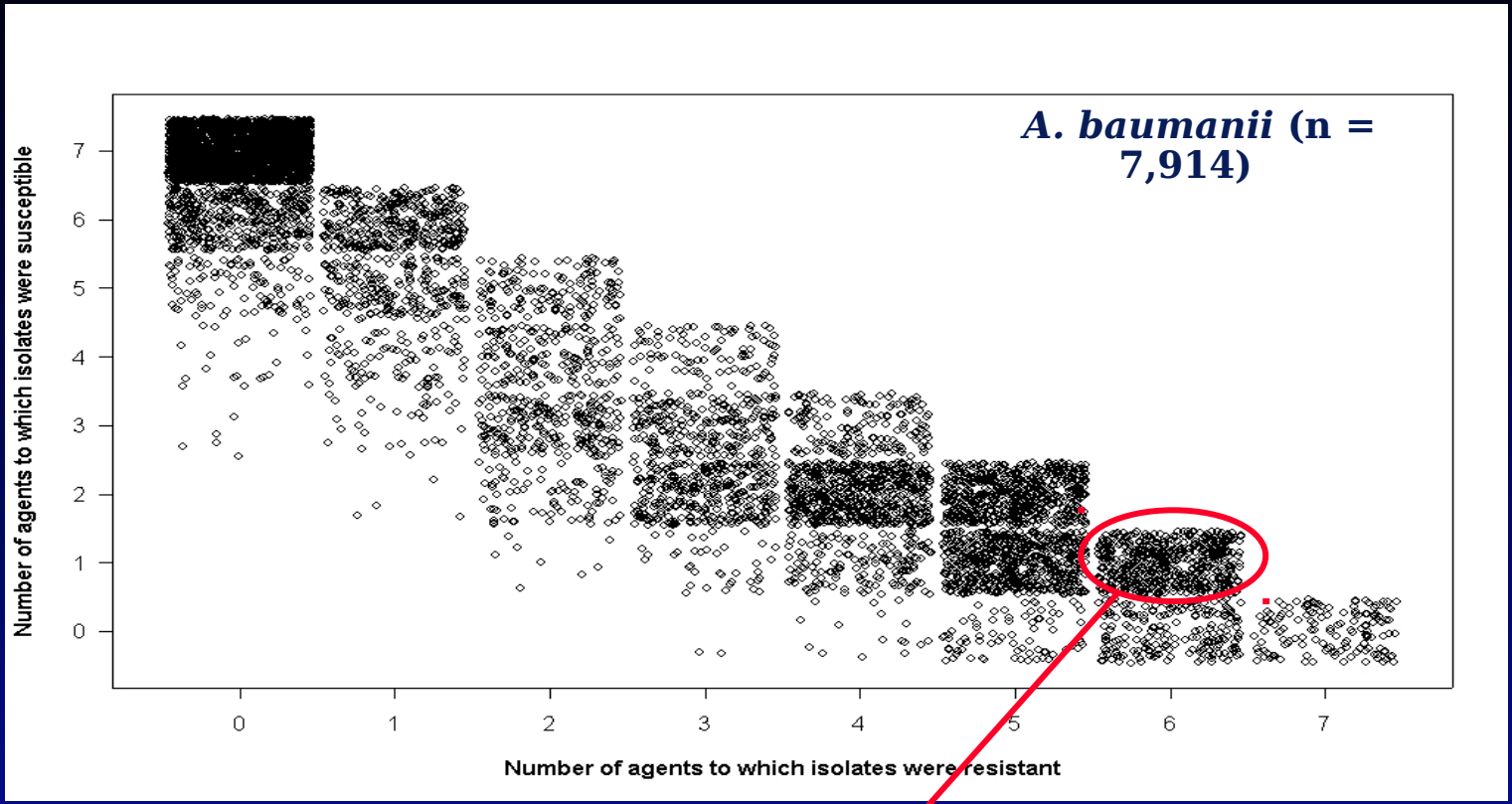



***Streptococcus pyogenes* (n = 701)**

**Antimicrobials = Penicillin, Vancomycin, Erythromycin, Clindamycin, Ceftriaxone, Levofloxacin**



# Detailed Analysis of Resistance Phenotypes




| | Percent of isolates resistant | | | | | | |
|---|---|---|---|---|---|---|---|
| Phenotype | Gentamicin | Ceftazidime | Imipenem | Ciprofloxacin | Cefepime | Ampicillin-sulbactam | Piperacillin |
| 1 drug resistance | 18.1 | 2.3 | 1 | 43.8 | 15.0 | 13.4 | 6.5 |
| 2 drug resistance | 75.5 | 7.7 | 1.9 | 80.4 | 20.9 | 6.1 | 7.5 |
| 3 drug resistance | 79.7 | 30.1 | 1.3 | 96.4 | 34.9 | 6.8 | 50.7 |
| 4 drug resistance | 79.2 | 63.7 | 3.3 | 97.0 | 55.7 | 14.4 | 86.7 |
| 5 drug resistance | 92.6 | 83.0 | 7.5 | 99.5 | 85.9 | 34.2 | 97.4 |
| 6 drug resistance | 98.0 | 91.1 | 28.3 | 99.2 | 97.8 | 86.2 | 99.5 |
| 7 drug resistance | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

# Antimicrobial Drug Development

## *The Future: Surveillance*

- **Future needs:**
  - **data on relating clinical outcomes to in vitro resistance is often lacking**
  - **obtaining patient level data often difficult and expensive**
  - **existing databases often do not allow determinations of accuracy of diagnosis, appropriateness of antimicrobial usage, reasons for antimicrobial usage, or accurate assessment of outcomes**

# Antimicrobial Drug Development

## *The Future: Prevention and Control*

- **FDA and CDC have undertaken "Get Smart" program to foster appropriate use**
- **Area of tension with pharmaceutical industry since this limits market**
- **Need data that appropriate use also associated with positive outcomes:**
  - **decreasing spread of resistant organisms**
  - **data that patient outcomes are similar or improved especially in less serious diseases**

# Antimicrobial Drug Development

## *The Future: Research*

- **Real and present need for clinical trials in areas that industry cannot or will not support**
- **Data on magnitude of benefit of antimicrobials in less serious self-resolving diseases**
  - **acute otitis media**
  - **acute bacterial sinusitis**
  - **acute exacerbations of chronic bronchitis**
  - **uncomplicated skin infections**
- **Data on efficacy of older, generic drugs against diseases due to some resistant pathogens**

# Antimicrobial Drug Development

## *The Future: Research*

- **Great need of rapid diagnostics**
  - **Clinical practice implications**
    - **guide appropriate use for patients who truly have bacterial disease**
    - **allow use of narrower spectrum agents with potential to limit spread of resistance**
  - **Clinical trials implications**
    - **allows screening and enrollment of fewer patients and increases efficiency of trials**
    - **makes narrower spectrum drugs easier to develop**

# Antimicrobial Drug Development

## *The Future: Product Development*

- **Greatest need is for discovery of new classes of antimicrobials**

- **Alterations in existing classes may still be helpful**
  - **need to concentrate on serious and life threatening diseases**
  - **recent examples of alterations in drug structure have also raised issues with drug safety**
    - **4 of 12 quinolones approved since 1980 have been withdrawn by the drug sponsors due to toxicity**

# Conclusions

- **Issues with drug discovery in antimicrobials have existed for 40 years**
- **Reasons why large companies are exiting antimicrobial drug development are primarily economic**
- **Tension between appropriate use and limiting the market**
- **Need for new drugs is greatest in serious and life threatening disease where market is smaller**

# Conclusions

- **Need for data on impact of in vitro resistance with clinical outcomes in various diseases**
- **Data on clinical impact of appropriate use strategies**
- **Clinical trials in self-resolving diseases and data on use of older generic drugs**
- **Development of rapid diagnostics**
- **New drug discovery**